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Planning and feasibility of phase III surgical trials in gynecologic oncology

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HIGHLIGHTS

- Retrospective consensus is a poor surrogate for clinical trials in surgical oncology.
- Community-level equipoise is essential; misjudging it compromises trial ethics and feasibility.
- Precise design is foundational: define the population, isolate the intervention, and anchor the endpoint.
- Feasibility testing is necessary to identify issues before full implementation.
- Strong patient preferences demand rigorous consent design in surgical trials.

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ABSTRACT

Surgical randomized controlled trials (RCTs) have fundamentally reshaped gynecologic oncology, yet surgical interventions remain far less likely than medical therapies to be supported by prospective evidence. This disparity arises not from a deficit of scientific ambition or a scarcity of clinically meaningful surgical questions but rather from the methodological constraints intrinsic to surgical research: operative variability across institutions and surgeons, operator-dependent outcome heterogeneity, and the difficulty of standardizing complex intraoperative decision-making. This article, the first in a three-part series on surgical trials in gynecologic oncology, addresses the pre-trial phase, the period when a clinical question evolves into a rigorously justified, ethical, and feasible phase III trial.

We examine five components of the trial planning process. First, we discuss equipoise, which refers to the genuine uncertainty among experts that must exist before a trial can be ethically justified, and this uncertainty gives shape and purpose to the trial design that follows. Second, we explore research questions which should precisely delineate the target population, clearly define the surgical intervention and comparator, and include a pre-specified primary endpoint that directly addresses the knowledge gap. Third, we distinguish between pilot and feasibility studies and argue that rigorous feasibility testing, including recruitment capacity, protocol adherence, regulatory infrastructure, randomization logistics, and surgeon credentialing, is foundational rather than optional. Third, we address the role of patient and stakeholder engagement, including the assessment of patient equipoise, the integration of patient-reported outcomes into endpoint selection, and the use of patient preference trial designs when strong a priori preferences exist. Fifth, we review the ethical and regulatory obligations unique to surgical trials, including the dual consent requirements for procedure and trial participation, and strategies for optimizing informed consent comprehension. These pre-trial decisions determine not only whether a surgical RCT can be launched, but whether it can be completed and ultimately transform care for patients with gynecologic malignancies.

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1. Introduction

Surgical randomized controlled trials (RCTs) have producing landmark findings in the field of gynecologic oncology, fundamentally reshaping surgical practice. Despite this impact, the surgical decision-making relies disproportionately on retrospective evidence. In fact, surgical interventions are less than half as likely as medical therapies to be supported by data derived from RCTs, a disparity that reflects not a lack of scientific ambition but the reality of structural challenges that make surgical trials difficult to design and execute well [1,2]. For example, operative outcomes are inherently sensitive to surgeons' skill, institutional resources, and equipment availability. The surgical encounter itself contains numerous possibilities for deviations from a standardized protocol, and these deviations are driven by surgeon judgment, individual anatomic variation, or intraoperative findings, which cannot fully be anticipated. These features make surgical RCTs both challenging and resource intensive.

The consequence of this evidence gap is not abstract. Surgical practice guided primarily by retrospective data is shaped by selection bias, confounding, and the preferences of high-volume treatment centers whose experience may not be generalizable. This phenomenon is encapsulated by the standard-of-care treatment in early-stage cervical cancer before the Laparoscopic Approach to Cervical Cancer (LACC) trial. Before this surgical trial, minimally invasive radical hysterectomy for early-stage cervical cancer had been widely adopted as the standard treatment and was included in the National Comprehensive Cancer Network (NCCN) guidelines based on retrospective studies laden with selection bias. However, the LACC trial, an RCT comparing open to minimally invasive radical hysterectomy for patients with early-stage cervical cancer, demonstrated shorter disease-free and overall survival for patients who underwent minimally invasive radical hysterectomy compared to those who underwent open surgery [3]. This experience demonstrates a scientific and clinical obligation to hold surgical practice to the same evidentiary standards as those for medical therapies.

As the first in a three-part series on surgical trials in gynecologic oncology, this article addresses the pre-trial phase: the period during which a surgical question evolves from a clinical question into a rigorously justified, ethically sound, appropriately designed, and operationally feasible phase III trial. This review focuses on the decisions that define this phase, including framing the research question, assessing feasibility, engaging stakeholders, and fulfilling ethical responsibilities, ultimately determine not only whether a trial can start, but whether it can be completed, it can meaningfully transform care for patients with gynecologic malignancies, and its findings can be trusted.

2. Establishing equipoise in gynecologic oncology

Every clinical trial originates from a research question, and the rigor with which that question is formulated governs the methodologic decisions that follow. In surgical oncology, a well-formed research question

must satisfy two simultaneous demands: scientific maturity, defined by a sufficient body of preliminary evidence to justify the prospective commitment of resources and patient participation, and clinical relevance, defined by the presence of a genuine knowledge gap. While simultaneous, these demands can also be competing: insufficient preliminary evidence undermines the scientific justification for randomization, yet sufficient data to resolve underlying uncertainty negates ethical basis, thus rendering a trial either premature or superfluous.

Randomization is ethically justified only when equipoise exists. Freedman defined equipoise as the state of genuine uncertainty among the expert community regarding the comparative effectiveness of the interventions under study [4]. Two features of Freedman's definition warrant emphasis. First, equipoise is a collective judgment of the clinical community rather than an individual judgment of an investigator. A researcher's personal uncertainty is insufficient if informed clinicians have reached a working consensus regarding treatment superiority. Second, equipoise functions as a threshold rather than a continuum. Meeting this threshold means that the expert community has no reliable evidentiary basis for preferring one intervention over another, justifying randomization because no patient is knowingly assigned an inferior treatment. When the threshold is not met, the ethical basis for randomization is absent. A lack of equipoise in RCTs has direct operational consequences, as patients and clinicians will systematically avoid the arm perceived as inferior, compromising enrollment and undermining the validity of the trial.

Establishing equipoise for a surgical trial requires a systematic and honest appraisal of the existing evidence. Retrospective analyses and population-based studies frequently provide the evidentiary foundation, establishing if existing data are insufficient to resolve the question of comparative effectiveness. The literature surrounding the LACC trial illustrates this process well. Prior retrospective data had demonstrated comparable recurrence and survival rates between minimally invasive and open radical hysterectomy for patients with early-stage cervical cancer, but no prospective studies addressed differences between these two surgical approaches definitively. That evidentiary landscape created the equipoise that made LACC trial both ethical and scientifically necessary, and the trial's findings, which ultimately demonstrated the inferiority of the minimally invasive approach, validated the importance of asking the question rigorously rather than allowing retrospective consensus to replace prospective evidence [3].

The consequences of misjudging equipoise run in both directions. The trial titled Omission of Lymphadenectomy in Advanced Epithelial Ovarian Cancer Patients Treated with Primary or Interval Cytoreductive Surgery (CARACO), was a phase III RCT in France that aimed to examine the use of retroperitoneal lymphadenectomy at the time of cytoreductive surgery. However, it was unable to achieve its recruitment goals and adequately enroll patients onto the trial after the publication of A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms (LION) [5,6]. Once the results of the LION trial became available, the equipoise underpinning the CARACO

trial dissolved. Investigators and patients could no longer genuinely regard the two arms as interchangeable, and enrollment plateaued. This sequence of events reflects not a failure of trial leadership, but rather the inherently dynamic nature of clinical equipoise and the obligation of investigators to monitor the evolving evidence landscape throughout a trial's conduct. It further underscores the importance of anticipating at the design stage which external developments might threaten equipoise and how the study protocol should respond to them. Regrettably, the CARACO trial is not an isolated case. Surgical trials face a disproportionate burden of premature closure, with early termination rates reported to be 44%–59% higher than those of nonsurgical trials [7]. Slow enrollment, inadequate funding, and insufficient institutional support are the most cited causes. These are challenges that are at common and partially addressable with careful planning.

One such planning element is the research question, which should be constructed so that it directly and precisely addresses the knowledge gap that generates equipoise between the trial arms. The degree to which the knowledge gap, the state of equipoise, and the formulation of the research question are brought into coherent alignment is among the most consequential determinants of trial integrity and scientific yield. A question that is broader than the uncertainty it is meant to address will produce findings that are difficult to interpret; one that is

narrower than the applicable uncertainty may neglect the clinical stakes that motivated the trial in the first place. Fig. 1 illustrates a framework for determining whether a clinical trial concept demonstrates equipoise. The clinical question should not only address the current knowledge gap and equipoise but also anticipate whether this question will still be relevant in the future. From the time of initial concept development of an RCT until its post-publication impact can span from 7 to 10 years with a median time from first participant enrollment until publication of 4.8 years [7]. Throughout this time, technology, parallel trials, and emerging therapeutics could render a trial obsolete before it is ever complete. Without a well thought out research question, the clinical trial may lack equipoise from the start.

3. Comparative surgical trial design: defining the question, intervention, and endpoints

The prevailing state of equipoise also governs the logical structure of the hypothesis under investigation. For example, a superiority framework is scientifically and ethically appropriate when genuine uncertainty exists regarding whether a novel intervention outperforms established practice. However, a non-inferiority design is instead appropriate when the clinical community operates under a working

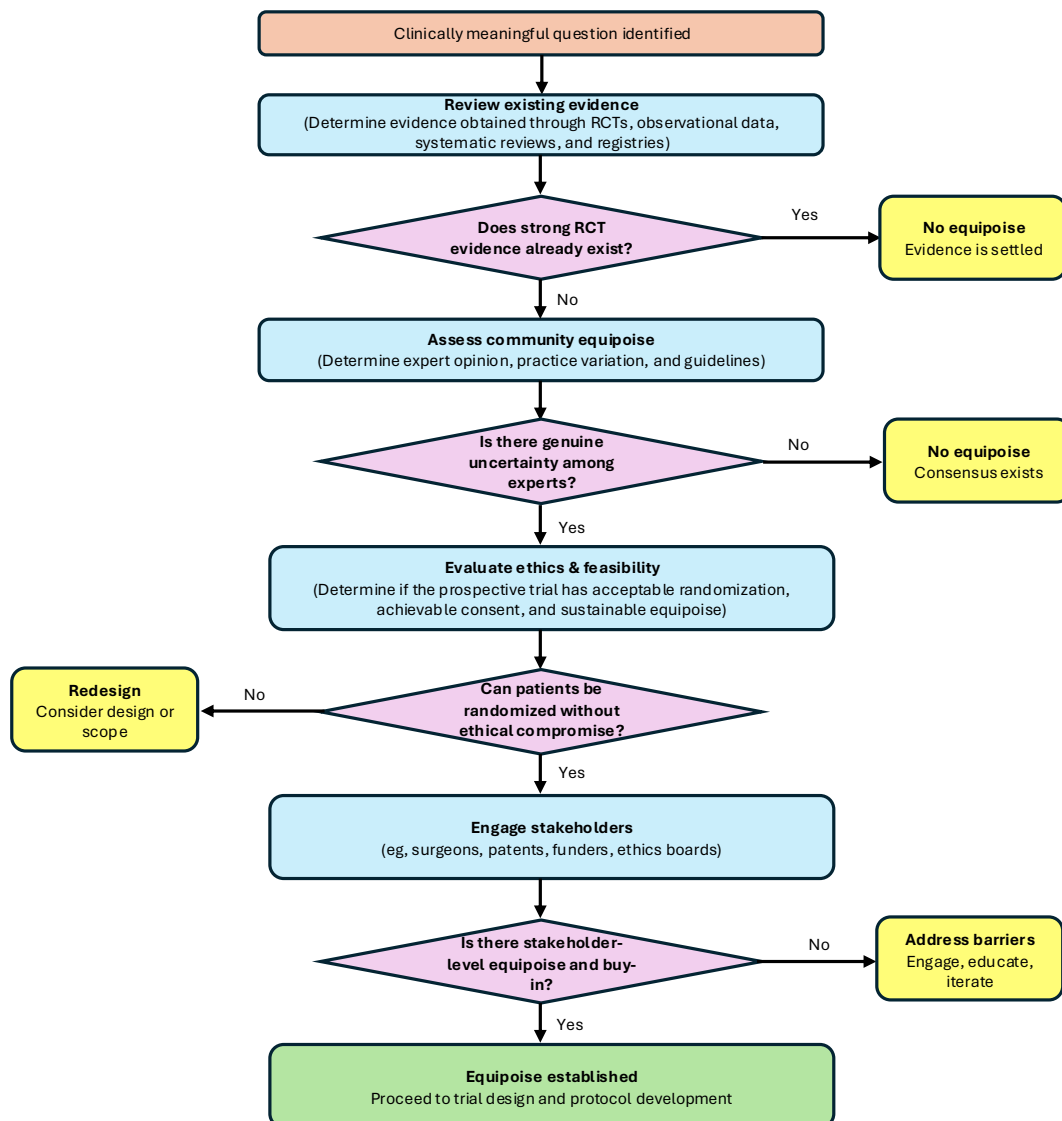


Fig. 1. Determining equipoise.

assumption of comparability and when the operative question is whether a less morbid approach preserves oncologic outcomes. Such design demands an explicitly pre-specified margin of acceptable inferiority, i.e., the threshold below which the intervention's reduced efficacy, if any, would remain clinically tolerable.

In gynecologic oncology, where surgical de-escalation is the dominant paradigm of contemporary trial activity, the distinction between a non-inferiority and superiority trial has material consequences. Misidentifying the appropriate approach as one addressed by a non-inferiority question rather than by a superiority question does not merely introduce statistical inefficiency; it fundamentally reframes the clinical question being posed, distorts the ethical justification for exposing patients to randomization, and compromises the actionability of the study's results. The hypothesis, in other words, is not a formality: it is the trial's governing logic, and its misspecification propagates error through every downstream decision. In gynecologic oncology, where surgical interventions vary widely in technique, operator experience, and patient selection, foundational step of developing the research question demands rigor and thoughtful assessment.

Firstly, developing the research question begins by carefully delineating the target population through eligibility criteria. Criteria that are too narrow strengthen internal validity by reducing heterogeneity but limit the generalizability of findings to broader clinical practice. Conversely, overly broad criteria may enhance external applicability but introduce confounding that obscures the true effect of the intervention. When developing a research question, the goal is to minimize selection bias while preserving sufficient generalizability so that trial results can meaningfully inform real-world care. An example of clear eligibility criteria are those included in the Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer (SHAPE) trial, which enrolled patients with the International Federation of Gynecology and Obstetrics stage IA2-IB1 cervical cancer but also included additional criteria: tumor size ≤ 2 cm, stromal invasion <10 mm on biopsy or less than 50% invasion on MRI, and no evidence of parametrial or nodal involvement on clinical exam or imaging [8]. By creating a strictly defined trial population that also generally describes most patients with low-risk, early-stage cervical cancer, the trial maximized internal validity without sacrificing substantial external generalizability. Investigators must be explicit and intentional in navigating this trade-off, as eligibility criteria will define both the population enrolled and the population for whom conclusions can be applicable.

Secondly, after defining the question in surgical trials, the intervention must be clearly defined and, whenever possible, limited to a single procedure or technical modification. The landmark LION trial exemplifies this principle, demonstrated by the isolation of systematic lymphadenectomy versus no lymphadenectomy as a discrete and testable surgical decision [9]. This singularity is essential; compound or bundled interventions make it impossible to attribute observed effects to any one component of the experimental arm. The comparator arm should reflect standard-of-care practice as it exists at the time of the trial, ensuring that the question being asked is clinically relevant and credible to the surgical community.

Thirdly, once the population and intervention are established, the trial must be anchored by a single, pre-specified primary endpoint. This endpoint must directly and unambiguously address the research question, and it serves as the organizing nexus for all major logistical decisions, including determining sample size, duration of follow-up, and the overall operational structure of the study. Critically, the outcome must be valid, objectively measurable, and defined in a manner that is resistant to investigator bias. Subjective or composite endpoints that allow for extensive interpretation undermine the scientific integrity of the trial and may render findings difficult to interpret. Once a primary endpoint has been defined, it is important to identify key secondary outcomes, which may allow investigators to explore related hypotheses, capture safety signals, and generate data to inform future research. However, secondary outcomes must also be well defined before

beginning the trial, and multiplicity testing must be conducted to avoid false positives, thus leading to drawing incorrect conclusions. Post-hoc identification of secondary outcomes raises the risk of data dredging and introduces bias that compromises the credibility of reported findings. A pre-specified secondary outcome plan, registered alongside the primary endpoint, reflects methodological transparency, strengthening the overall quality of the trial.

4. Defining and testing feasibility

Before initiating a large-scale RCT, investigators must rigorously assess the trial's feasibility as designed. Feasibility testing serves this purpose, allowing investigators to identify and address obstacles related to recruitment, outcome measurement, and randomization before committing the resources required for a definitive trial. In surgical trials where operative variability, institutional heterogeneity, and patient selection introduce complexity absent in therapeutic drug trials, feasibility testing is foundational to the process.

Pilot studies and feasibility studies are related but distinct and conflating them carries meaningful consequences for surgical trial planning. A pilot study, in its conventional use, demonstrates that a trial can be conducted—albeit at a reduced scale—but does not systematically examine the ways in which the full-scale design might fail. A feasibility study is broader in scope and more analytically rigorous, designed to identify and address the specific uncertainties that could compromise a larger RCT before such uncertainties manifest at scale [9].

In a 2023 systematic review, Cousins et al. examined how pilot and feasibility studies inform randomized placebo-controlled surgical trials and concluded that well-designed feasibility studies, which are more extensive than simple pilot studies, resolve uncertainties and determine optimal study design prospectively, helping overcome the distinct challenges of surgical RCTs [10]. Guidelines for improved reporting of pilot and feasibility studies have been published, including an extension to the Consolidated Standards of Reporting Trials (CONSORT) statement, and a more recent conceptual framework has emerged to define the purpose and scope of these studies in preparation for RCTs. However, no specific recommendations exist specifically for their application to surgical trials [9,11,12]. This gap underscores both the importance and the underdevelopment of this area in the surgical literature.

The scope of a feasibility study must be carefully defined. Its primary focus should be the operational and structural uncertainties that could undermine a larger trial, such as 1) the ability of the study to recruit patients at the anticipated rate, 2) the consistency and precision of the delivery of the comparator and experimental arms, 3) determining any necessary blinding challenges, and 4) the practicality of the timing and process of randomization within the clinical workflow. Addressing these uncertainties requires success criteria that are pre-specified before the feasibility study begins. Each operational domain requires measurable thresholds (i.e., a minimum monthly accrual rate, a maximum protocol deviation rate, and an acceptable conversion rate) allowing for structured go/no-go decisions.

An example of a RCT that prospectively addressed such uncertainties is the Laparoscopic Cytoreduction after Neoadjuvant Chemotherapy in High-Grade Epithelial Ovarian Cancer (LANCE) trial, which is an ongoing RCT examining the safety and efficacy of a minimally invasive approach for ovarian cancer cytoreductive surgery compared to an open technique [13]. In the LANCE trial lead-in phase, investigators prospectively specified three criteria before initiating the full-scale trial, ensuring that the determination of the feasibility of the trial was evidence-based rather than subjective. The feasibility questions accounted for accrual rate, conversion to laparotomy rate, and a difference in the complete gross resection rate of less than 20 percentage points. These questions allowed the trial investigators to determine that a full-scale surgical trial was not only necessary but feasible in the given time period with appropriate surgeons.

Critically, feasibility studies should not be designed or interpreted as tests of intervention effectiveness. Rather, the feasibility phase exists to optimize trial architecture. Using an underpowered preparatory study to evaluate clinical outcomes can lead to misleading conclusions that may inappropriately dissuade the pursuit of a larger, definitive trial or, conversely, generate false reassurance. Investigators should also use the feasibility phase to develop a principled approach to assess participating surgeons and institutions. Variability in operative skill and institutional volume are intrinsic features of surgical research, and the feasibility period offers the opportunity to evaluate credentialing criteria, determine minimum volume thresholds, and assess whether the technical standardization required for a valid trial is achievable across the intended sites.

In addition to the opportunity to define these quantitative components, a feasibility study can also be used to identify qualitative components. Interviews, focus groups, and surveys offer a complementary and underutilized means of examining the design and acceptability of a trial from the perspective of all stakeholders, including patients, surgeons, coordinators, and institutional leaders. This qualitative work can help uncover concerns about randomization acceptability, equipoise, patient preferences, and logistical barriers that may not be apparent to the principal investigator and that may not be captured by recruitment rates or protocol deviation counts alone. Integrating these methods into the feasibility phase provides a richer and more complete picture of whether a trial is ready to proceed at scale and may identify modifications to improve both the final design's rigor and acceptability.

Additionally, other feasibility components must be prospectively addressed during this planning phase. First, early and sustained biostatistician involvement is essential, not merely for sample size estimation but also for defining the minimally clinically important difference, constructing a pre-specified statistical analysis plan, and establishing principled approaches to screen failures, missing data, and any planned exploratory analyses. The relationship between statistician and investigator must be collaborative and iterative from the outset, not consultative at the point of manuscript preparation. Second, and equally important, a formal credentialing protocol governing surgeon participation should be developed. Without explicit operability criteria, heterogeneity in operator experience becomes an uncontrolled source of outcome variance, possibly obscuring true treatment effects and undermining the internal validity of the trial. At minimum, the credentialing framework should define a minimum case volume threshold, enumerate required training materials (eg, operative manuals, procedural checklists, and annotated surgical videos), and specify whether a supervised proctoring period must be completed before a site may begin enrolling patients. Establishing these standards prospectively serves a dual function: it sets transparent expectations for participating sites and maximizes the likelihood that the intervention is delivered with sufficient fidelity to render the results interpretable and generalizable.

5. Stakeholder and patient advocate engagement

Although necessary, sound methodology and operational feasibility alone are insufficient to develop a successful surgical RCT. Trials are conducted by surgeons, administered by coordinators, and depend on patients (and their enrollment). Each of these groups brings expectations, preferences, and constraints that shape how a trial performs in practice. Engaging these stakeholders early and deliberately is not a peripheral concern but a determinant of whether the trial can recruit and retain patients and ultimately answer the question it was designed to address.

One of the most consequential and underappreciated challenges in surgical trial design is the impact of patient preferences. When patients hold strong *a priori* preferences for one treatment arm, enrollment is compromised, randomization becomes contentious, and those who do enroll may not be representative of the broader population the trial

intends to study. This challenge is less prominent in trials of systemic therapy when a new intervention (eg, a new drug) is only available within a study, which is usually not the case for a surgical trial. In gynecologic oncology, this challenge takes on different forms depending on the nature of the intervention being tested.

Trials in which one arm has no surgical intervention or omits a procedure that patients perceive as protective can be especially plagued by this challenge. The Study Comparing Tumor Debulking Surgery Versus Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer (DESKTOP III) trial, a phase III trial of patients with recurrent platinum-sensitive ovarian cancer, illustrates this challenge well: researchers asked patients facing a cancer relapse to accept randomization to surgery with chemotherapy or chemotherapy alone, with the latter treatment requiring the omission of secondary cytoreductive surgery that patients may have perceived as offering a meaningful chance at improved disease control despite the absence of definitive evidence supporting its positive impact at the time of trial design [14]. The trial ultimately enrolled 407 women across 80 centers in 12 countries between 2010 and 2014, requiring a recruitment effort spanning years and broad international collaboration, reflecting the difficulty of accruing patients willing to accept the chemotherapy-only arm. Conversely, trials requiring acceptance of an additional or novel surgical intervention may face resistance from patients who prefer the familiarity and perceived safety of established practice (eg, the LANCE trial, which faced challenges owing to some countries perceiving minimally invasive surgery in ovarian cancer as experimental). Both scenarios can distort enrollment patterns and threaten the internal validity of the trial if not anticipated and addressed in the planning phase.

Trial planning in surgery has traditionally focused on surgeon equipoise, the genuine uncertainty among operating physicians about which approach is superior, as the ethical and scientific justification for randomization. Although necessary, surgeon equipoise is not sufficient: patient equipoise must be assessed with equal rigor. A trial that has surgeon equipoise but lacks patient equipoise will face recruitment challenges that no amount of operational optimization can fully overcome. Investigators must therefore evaluate the degree to which potential participants view the treatment arms as genuinely interchangeable and must design consent processes and patient-facing materials that honestly communicate uncertainty without inadvertently steering preferences in one direction.

A related and frequently neglected dimension of stakeholder engagement is how patients value the outcomes being measured. The extent to which a difference in an objective endpoint, such as a recurrence or a survival interval, actually matters to a patient is a question that are rarely directly included in trial designs. Instead, the threshold for clinical significance is typically determined by expert consensus, with investigators and statisticians defining what constitutes a meaningful treatment difference based on professional judgment and precedent set by previous trials. This approach has well-documented limitations. Patients and clinicians often weigh trade-offs differently, assign different relative importance to outcomes, and prioritize distinct aspects of treatment experience. A treatment effect that reaches the threshold of clinical significance as defined by experts may fall below the threshold of meaningful benefit as defined by patients—or vice versa. For example, inguinal lymphadenectomy for the treatment of vulvar cancer has a high complication rate including wound breakdown, infection, and lifelong lymphedema, which can be debilitating for patients [15,16]. The GROningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V I), one of the trials examining sentinel lymph node biopsy for vulvar cancer, allowed patients with a negative sentinel lymph node biopsy to omit full inguinal lymphadenectomy, which was enticing for patients who wanted to avoid the severe morbidity associated with the more extensive procedure [17]. However, the trial also risked a negative oncologic outcome by omitting the full lymph node dissection thereby missing a positive lymph node, which may have excluded patients who desired the most aggressive surgical approach despite the

possible complications. Additionally, many institutions are increasingly directing funding toward trials that emphasize patient-reported outcomes. The Patient-Centered Outcomes Research Institute, for example, specifically funds research on comparative effectiveness of outcomes meaningful to patients and requires active patient and stakeholder engagement throughout the research process. The incorporation of patient-reported outcome measures, the inclusion of exercises to clarify values, and incorporating direct stakeholder input into the definition of clinically important differences are more valid and reliable approaches to ensuring that trial endpoints reflect what actually matters to those the research is designed to serve (ie, the patients).

When patient preferences are particularly strong or heterogeneous, a conventional randomized design may not be the most appropriate or feasible structure for a trial. Patient preference trials offer an alternative framework that explicitly accommodates preference as a variable rather than treating it as a source of bias to be minimized. In the patient preference trial design, patients who express a strong preference for one treatment arm are permitted to receive it outside of randomization, and those with genuine equipoise are conventionally randomized. This approach preserves the randomized component for those most suited to it while generating complementary data from the preference cohorts that can enrich interpretation of the overall findings. The Tubectomy with delayed oophorectomy as Alternative for risk-reducing salpingo-oophorectomy in high-risk Women to assess the Safety of Prevention (TUBA-WISP II) trial is an example of this trial design in a gynecologic oncology context, illustrating how preference-accommodating frameworks can be operationalized in practice. In this prospective surgical trial, patients harboring germline *BRCA* mutations can opt for definitive risk-reducing salpingo-oophorectomy in the recommended age range or elect for bilateral salpingectomy with delayed oophorectomy [18]. As surgical trials increasingly involve interventions where patient perspectives on risk, recovery, and quality of life are central to treatment decisions, the patient preference trial design warrants serious consideration during feasibility planning. However, the level of evidence such trials generate remains poorly defined, and this design may be better suited to a dual cohort framework than a traditional randomized trial. Importantly, several methodological limitations cannot be overlooked. Allowing patients to self-select their treatment arm introduces substantial risk of selection bias and confounding, risks unequal group sizes, and ultimately compromises both internal validity and generalizability.

Patient recruitment is equally critical to trial success—approximately 50% of surgical RCTs fail to complete due to inadequate recruitment [19]. Engaging patient partners in trial design and the development of recruitment materials has been shown to improve both recruitment and retention in oncology trials [20]. Incorporating patient perspectives ensures that materials are accessible, understandable, and appealing to potential participants. Recruitment strategies should also be iteratively refined throughout the trial based on structured feedback from participants and recruiters. Without adequate recruitment, even the most rigorously designed trial cannot succeed, and this element deserves the same deliberate attention as the intervention and analytic plan.

6. Regulatory and ethical preparation

Ethical preparation for surgical trials demands a level of attention greater than that required for conventional therapeutic drug trials. The invasive nature of surgical interventions and the irreversibility of operative decisions create an ethical landscape that investigators must navigate with care, transparency, and a thorough grounding in the relevant literature and regulatory frameworks [21].

Surgical trials differ from therapeutic drug trials in ethically noteworthy ways. In escalation trials, patients are exposed to an invasive procedure whose incremental benefit over standard care remains uncertain, a risk that is accepted in exchange for the possibility of improved outcomes, as shown in the aforementioned DESKTOP III trial.

In de-escalation trials, as in the aforementioned LION trial, the calculus is reversed: a potentially beneficial intervention is withheld from one arm of the study, raising the prospect that patients randomized to the less aggressive approach may be denied a treatment that could have helped them. This tension is particularly acute in gynecologic oncology, where surgical staging and cytoreductive procedures carry both therapeutic intent and diagnostic value, and where the consequences of under-treatment can be significant. These distinctive features require that the ethical justification for the trial design be explicit and rigorous, and researchers should revisit the ethics justification of the trial at each stage of development and execution.

Consent for surgical trials is inherently more complex than consent for therapeutic drug trials because investigators must address two distinct but intertwined patient consents simultaneously: consent for the surgical procedure itself and consent for trial participation. Full disclosure is non-negotiable. Patients must understand how each arm of the trial compares to standard of care and what they may gain or forgo by participating. For example, in the LANCE trial, patients in the experimental arm stand to benefit from a minimally invasive surgical approach even in the absence of certainty about oncologic non-inferiority, a potential advantage that must be communicated alongside the uncertainty it accompanies. At the same time, the genuine scientific question behind the trial (i.e., whether open surgery is truly necessary or not to achieve equivalent oncologic outcomes in a select patient population) must be conveyed in a way that makes the rationale for randomization credible and comprehensible to a non-specialist [13].

Several strategies have been shown to improve patient understanding during the surgical trial consent process. Longer discussion time between patient and provider, consent obtained by the operating surgeon rather than an independent researcher, and simplified consent forms developed with input from patient advocates all improve patient and caregiver comprehension [22,23]. Poor consent comprehension is an ethical failure, not just a procedural shortcoming. A consent process that leaves patients uncertain about what they have agreed to undermines the concept of free will that gives informed consent its moral force, and in the context of surgical trials, where the stakes of misunderstanding are high, this standard must be met with rigor.

Beyond consent, several regulatory obligations must be addressed prospectively. Prospective trial registration in a publicly accessible registry, such as [ClinicalTrials.gov](https://clinicaltrials.gov), is a prerequisite for publication in most high-impact journals and a foundational transparency requirement. In other words, many journals will not consider publishing a trial's results if the trial is not registered in [ClinicalTrials.gov](https://clinicaltrials.gov). A pre-specified data-sharing plan must be developed at the design stage as they are often required by governing as well as funding bodies. Finally, for multicenter trials, which represent the majority of phase III surgical RCTs in gynecologic oncology, coordinating approvals across multiple institutional review boards, whether local, national, or international, is among the most common sources of activation delay and should be planned explicitly, with consideration given to centralized review mechanisms where available.

7. Conclusion

The pre-trial phase is not preparatory work that precedes a surgical RCT; it is the foundation on which a surgical RCT is built. Decisions made before the first patient is enrolled determine whether the research question is answerable, whether the trial can recruit and retain participants, and whether the findings will be valid and generalizable. Errors in this phase do not stay contained but move into other phases as recruitment failures, protocol deviations, and consent inadequacies emerge, ultimately compromising the integrity and applicability of the results. The five components addressed in this article reflect this reality: equipoise, research question formulation, feasibility testing, stakeholder engagement, and ethical preparation are not bureaucratic checkpoints but the scientific and ethical substance of surgical trial design.

The distinctive challenges of surgical research, including operative variability, operator-dependent outcomes, and the layered consent obligations of invasive procedures, do not exempt the field from the standards of evidence-based medicine. They demand a more deliberate application of those standards. Feasibility testing is a scientific obligation, not an administrative formality. Patient preferences and patient-reported outcomes must be integrated into endpoint selection from the outset. Consent processes require the same strictness as does the surgical protocol itself. The ethical framework underpinning the trial must be monitored continuously, not established once and assumed to hold.

The subsequent articles in this series address trial execution and the reporting of surgical RCT findings. A surgical trial that is well-planned but poorly executed delivers incomplete answers; one that is well-executed but poorly reported delivers answers that cannot be used. The pre-trial decisions described in this article are the first link in a chain that must hold at every point if a surgical RCT is to generate evidence that changes practice, reduces harm, and ultimately improves outcomes for patients with gynecologic malignancies.

CRediT authorship contribution statement

Alexandra S. Bercow: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Nuria Agusti:** Writing – review & editing, Investigation, Conceptualization. **Pedro Ramírez:** Writing – review & editing, Conceptualization. **Anne Knisely:** Writing – review & editing, Investigation. **Marie Plante:** Writing – review & editing, Conceptualization. **Philipp Harter:** Writing – review & editing, Conceptualization. **Anna Fagotti:** Writing – review & editing, Conceptualization. **Andreas Obermair:** Writing – review & editing, Conceptualization. **J. Alejandro Rauh-Hain:** Writing – review & editing, Investigation, Conceptualization.

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References

- [1] M.J. Solomon, R.S. McLeod, Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 118 (1995) 459–467, [https://doi.org/10.1016/s0039-6060\(05\)80359-9](https://doi.org/10.1016/s0039-6060(05)80359-9).
- [2] F. Farrokhyar, P.J. Karanickolas, A. Thoma, M. Simunovic, M. Bhandari, P.J. Devereaux, M. Anvari, A. Adili, G. Guyatt, Randomized controlled trials of surgical interventions, *Ann. Surg.* 251 (2010) 409–416, <https://doi.org/10.1097/SLA.0b013e3181cf863d>.
- [3] P.T. Ramirez, M. Frumovitz, R. Pareja, A. Lopez, M. Vieira, R. Ribeiro, A. Buda, X. Yan, Y. Shuzhong, N. Chetty, D. Isla, M. Tamura, T. Zhu, K.P. Robledo, V. Gebisi, R. Asher, V. Behan, J.L. Nicklin, R.L. Coleman, A. Obermair, Minimally invasive versus abdominal radical hysterectomy for cervical cancer, *N. Engl. J. Med.* 379 (2018) 1895–1904, <https://doi.org/10.1056/NEJMoa1806395>.
- [4] B. Freedman, Equipoise and the ethics of clinical research, *N. Engl. J. Med.* 317 (1987) 141–145, <https://doi.org/10.1056/NEJM198707163170304>.
- [5] P. Harter, J. Sehouli, D. Lorusso, A. Reuss, I. Vergote, C. Marth, J.-W. Kim, F. Raspagliesi, B. Lampe, G. Aletti, W. Meier, D. Cibula, A. Mustea, S. Mahner, I.B. Runnebaum, B. Schmalfeldt, A. Burges, R. Kimmig, G. Scambia, S. Greggi, F. Hilpert, A. Hasenburger, P. Hillemanns, G. Giorda, I. Von Leffern, C. Schade-Brittinger, U. Wagner, A. Du Bois, A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms, *N. Engl. J. Med.* 380 (2019) 822–832, <https://doi.org/10.1056/NEJMoa1808424>.
- [6] J.-M. Classe, E. Cerato, C. Boursier, J. Dauplat, C. Pomel, R. Villet, J. Cuisenier, G. Lorimier, J.-F. Rodier, P. Mathevet, G. Houvenaghel, J. Leveque, F. Lécure, Impact des curages rétropéritonéaux sur la survie des patientes atteintes d'un cancer de l'ovaire à un stade avancé : le protocole CARACO, *J. Gynecol. Obstet. Biol. Reprod.* 40 (2011) 201–204, <https://doi.org/10.1016/j.jgyn.2011.02.009>.
- [7] C. Shadbolt, E. Naufal, S. Bunzli, V. Price, S. Rele, C. Schilling, S. Thuraingam, L.S. Lohmander, Z.J. Balogh, P. Clarke, P. Choong, M. Dowsey, Analysis of rates of completion, delays, and participant recruitment in randomized clinical trials in surgery, *JAMA Netw. Open* 6 (2023) e2250996, <https://doi.org/10.1001/jamanetworkopen.2022.50996>.
- [8] M. Plante, J.S. Kwon, S. Ferguson, V. Samouëlian, G. Ferron, A. Maulard, C. De Kroon, W. Van Driel, J. Tidy, K. Williamson, S. Mahner, S. Kommos, F. Goffin, K. Tamussino, B. Eyjólfssdóttir, J.-W. Kim, N. Gleeson, L. Brotto, D. Tu, L.E. Shepherd, Simple versus radical hysterectomy in women with low-risk cervical cancer, *N. Engl. J. Med.* 390 (2024) 819–829, <https://doi.org/10.1056/NEJMoa2308900>.
- [9] S.M. Eldridge, G.A. Lancaster, M.J. Campbell, L. Thabane, S. Hopewell, C.L. Coleman, C.M. Bond, Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework, *PLoS One* 11 (2016), e0150205, <https://doi.org/10.1371/journal.pone.0150205>.
- [10] S. Cousins, A. Gormley, K. Chalmers, M.K. Campbell, D.J. Beard, N.S. Blencowe, J.M. Blazeby, How do pilot and feasibility studies inform randomised placebo-controlled trials in surgery? A systematic review, *BMJ Open* 13 (2023), e071094, <https://doi.org/10.1136/bmjopen-2022-071094>.
- [11] K. Fairhurst, J.M. Blazeby, S. Potter, C. Gamble, C. Rowlands, K.N.L. Avery, Value of surgical pilot and feasibility study protocols, *Br. J. Surg.* 106 (2019) 968–978, <https://doi.org/10.1002/bjs.11167>.
- [12] S.M. Eldridge, C.L. Chan, M.J. Campbell, C.M. Bond, S. Hopewell, L. Thabane, G.A. Lancaster, CONSORT 2010 statement: extension to randomised pilot and feasibility trials, *BMJ* (2016), i5239, <https://doi.org/10.1136/bmj.i5239>.
- [13] J.A. Rauh-Hain, A. Melamed, R. Pareja, T. May, A. Sinno, L. McNally, N.S. Horowitz, P. De Iaco, C.M. Michener, L. Van Lonkhuijzen, M.D. Iniesta, Y. Yuan, P.T. Ramirez, A. Fagotti, Laparoscopic cytoreduction after neoadjuvant chemotherapy in high-grade epithelial ovarian Cancer: a LANCE randomized clinical trial, *JAMA Netw. Open* 7 (2024), e2446325, <https://doi.org/10.1001/jamanetworkopen.2024.46325>.
- [14] P. Harter, J. Sehouli, I. Vergote, G. Ferron, A. Reuss, W. Meier, S. Greggi, B.J. Mosgaard, F. Selle, F. Guyon, C. Pomel, F. Lécure, R. Zang, E. Avall-Lundqvist, J.-W. Kim, J. Ponce, F. Raspagliesi, G. Kristensen, J.-M. Classe, P. Hillemanns, P. Jensen, A. Hasenburger, S. Ghaem-Maghani, M.R. Mirza, B. Lund, A. Reinthaller, A. Santaballa, A. Olaitan, F. Hilpert, A. Du Bois, Randomized trial of cytoreductive surgery for relapsed ovarian Cancer, *N. Engl. J. Med.* 385 (2021) 2123–2131, <https://doi.org/10.1056/NEJMoa2103294>.
- [15] J.W. Carlson, J. Kauderer, A. Hutson, J. Carter, J. Armer, S. Lockwood, S. Nolte, B.R. Stewart, L. Wenzel, J. Walker, A. Fleury, A. Bonebrake, J. Soper, C. Mathews, O. Zivanovic, W.E. Richards, A. Tan, D.S. Alberts, R.R. Barakat, GOG 244-the lymphedema and gynecologic cancer (LEG) study: incidence and risk factors in newly diagnosed patients, *Gynecol. Oncol.* 156 (2020) 467–474, <https://doi.org/10.1016/j.ygyno.2019.10.009>.
- [16] A. Wills, A. Obermair, A review of complications associated with the surgical treatment of vulvar cancer, *Gynecol. Oncol.* 131 (2013) 467–479, <https://doi.org/10.1016/j.ygyno.2013.07.082>.
- [17] A.G.J. Van der Zee, M.H. Oonk, J.A. De Hullu, A.C. Ansink, I. Vergote, R.H. Verheijen, A. Maggioni, K.N. Gaarenstroom, P.J. Baldwin, E.B. Van Dorst, J. Van der Velden, R.H. Hermans, H. van der Putten, P. Drouin, A. Schneider, W.J. Sluiter, Sentinel node dissection is safe in the treatment of early-stage vulvar cancer, *J. Clin. Oncol.* 26 (2008) 884–889, <https://doi.org/10.1200/JCO.2007.14.0566>.
- [18] M.P. Steenbeek, M.H.D. van Bommel, J. int'Hout, C.B. Peterson, M. Simons, K.C.B. Roes, M. Kets, B.M. Norquist, E.M. Swisher, R.P.M.G. Hermens, TUBA-WISP II consortium, K.H. Lu, J.A. de Hullu, TUBectomy with delayed oophorectomy as an alternative to risk-reducing salpingo-oophorectomy in high-risk women to assess the safety of prevention: the TUBA-WISP II study protocol, *Int. J. Gynecol. Cancer* 33 (2023) 982–987, <https://doi.org/10.1136/ijgc-2023-004377>.
- [19] M.M. Ninomiya, J. Hiemstra, E. Nicholson, K.V. Isaac, Methods of recruitment for surgical and perioperative randomized controlled trials: a rapid review, *World J. Surg.* 47 (2023) 2659–2667, <https://doi.org/10.1007/s00268-023-07124-z>.
- [20] J. Needham, J. Taylor, D. Nomikos, Integrating patient-centred research in the Canadian cancer trials group, *Curr. Oncol.* 28 (2021) 630–639, <https://doi.org/10.3390/curroncol28010062>.
- [21] D.J. Beard, M.K. Campbell, J.M. Blazeby, A.J. Carr, C. Weijer, B.H. Cuthbertson, R. Buchbinder, T. Pinkney, F.L. Bishop, J. Pugh, S. Cousins, I.A. Harris, L.S. Lohmander, N. Blencowe, K. Gillies, P. Probst, C. Brennan, A. Cook, D. Farrar-Hockley, J. Savulescu, R. Huxtable, A. Rangan, I. Tracey, P. Brocklehurst, M.L. Ferreira, J. Nicholl, B.C. Reeves, F. Hamdy, S.C. Rowley, J.A. Cook, Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines),

- Lancet 395 (2020) 828–838, [https://doi.org/10.1016/S0140-6736\(19\)33137-X](https://doi.org/10.1016/S0140-6736(19)33137-X).
- [22] S.A. Acuna, T.R. Chesney, N.N. Baxter, Incorporating patient preferences in noninferiority trials, JAMA 322 (2019) 305, <https://doi.org/10.1001/jama.2019.7059>.
- [23] A. Nishimura, J. Carey, P.J. Erwin, J.C. Tilburt, M.H. Murad, J.B. McCormick, Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials, BMC Med. Ethics 14 (2013) 28, <https://doi.org/10.1186/1472-6939-14-28>.